Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency

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INTRODUCTION — Alpha-1 antitrypsin (AAT) deficiency is a clinically under-recognized inherited disorder affecting the lung, liver, and rarely skin. The characteristics of the pulmonary manifestations of this disorder will be reviewed here [1-4]. Extrapulmonary disease and therapy are discussed separately. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency" and "Treatment of alpha-1 antitrypsin deficiency".)

AAT PHENOTYPES — AAT is a protease inhibitor (encoded by the gene PI, MIM +107400) of the proteolytic enzyme elastase. It is part of a larger family of structurally unique serine protease inhibitors, referred to as serpins, which have been implicated in the pathogenesis of neurodegenerative diseases, angioedema, and coagulation abnormalities [1,5]. At least 100 alleles of AAT have been identified and given a letter code based upon electrophoretic mobility. They can be categorized into four basic groups:

Normal — Normal alleles are associated with normal levels of AAT and normal function. The family of normal alleles is referred to as M and the normal phenotype is MM.

Deficient — Deficient alleles are associated with plasma AAT levels less than 35 percent of the average normal level. The most common deficient allele associated with emphysema is the Z allele, which is carried by approximately 2 to 3 percent of the Caucasian population in the United States.

Null — Null alleles lead to no detectable AAT protein in the plasma. Individuals with the null phenotype are the least common and have the most severe form of the disease.

Dysfunctional — Dysfunctional alleles produce a normal quantity of AAT protein

but the protein does not function properly (eg, PI*F).

Population studies suggest a minimum plasma threshold of 11 µmol per L (corresponding to 50 to 80 mg per dL, depending on the assay used), below which there is insufficient AAT to protect the lung, leading to an increased risk of developing emphysema. Most patients below this threshold level have the PI*Z phenotype (ie, homozygous PI*ZZ) (table 1) [6].

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

EPIDEMIOLOGY — Although AAT deficiency is commonly considered to be rare, estimates that 80,000 to 100,000 individuals in the United States have severe deficiency of AAT suggest that the disease is under-recognized [7,8]. The prevalence of AAT varies considerably from one country to another; however, it is estimated that more than 3 million people worldwide have allele combinations associated with severe deficiency [9,10].

Prevalence — Two lines of evidence support prevalence estimates indicating that AAT deficiency is approximately as common as cystic fibrosis:

- One study evaluated a sample of 965 patients with chronic obstructive pulmonary disease (COPD); severe deficiency of AAT was found in 2 to 3 percent [11]. Extrapolating to the United States population of 2.1 million individuals with emphysema (based on the National Health Interview Survey [12]), 40,000 to 60,000 Americans would be expected to have emphysema caused by AAT deficiency.
- Direct population screening studies indicate that the prevalence of individuals with severe deficiency of AAT (ie, PI*Z phenotype) ranges from one in 1575 to one in 5097 individuals [13-16]. Based upon the United States population of approximately 250 million, 80,000 to 100,000 severely AAT deficient individuals would be expected. This estimate includes both symptomatic and asymptomatic patients.

Unrecognized deficiency — Several studies indicate that AAT deficiency is far less familiar to many clinicians than its prevalence would suggest. Investigators in one report, for example, estimated that there were 700 PI*ZZ individuals in St. Louis, based upon sampling of 20,000 blood specimens submitted to the St. Louis blood bank; only 28 of these individuals (4 percent) had been identified [15]. Unrecognized individuals with severe deficiency of AAT probably comprise two separate groups: those with no clinical manifestations despite severe deficiency;

and those with disease in whom the underlying AAT deficiency has been unrecognized. The relative proportion of these two groups remains unknown.

Under-recognition of AAT deficiency has also been demonstrated [7,8,17]. A poll of 304 individuals with severe deficiency of AAT indicated an average delay of 7.2 years between the first onset of symptoms and the diagnosis of AAT deficiency. Furthermore, 43 percent of respondents reported seeing at least three clinicians and 12 percent reported seeing between 6 and 10 clinicians before the diagnosis of AAT deficiency was first made. Two more recent surveys demonstrated that the delay between the first symptom and recognition of AAT deficiency had not decreased [7,8], indicating that under-recognition persists despite extensive educational efforts and the publication of evidence-based guidelines for diagnosis and management of AAT deficiency [4].

CLINICAL MANIFESTATIONS — The main clinical manifestations relate to three separate organs: the lung, the liver, and much less often the skin. Sporadic reports indicate other clinical conditions also may accompany AAT deficiency. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency".)

In the lung, severe deficiency of AAT predisposes to chronic obstructive pulmonary disease, especially **panacinar emphysema** (picture 1A-B) [18,19]. Some series also report an association of AAT deficiency with bronchiectasis and/or asthma, but these relationships have not been as firmly established [20].

Emphysema in AAT deficiency is thought to result from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin.

The pathogenesis of the liver disease is quite different. Only those phenotypes associated with pathologic polymerization of AAT within the endoplasmic reticulum of hepatocytes produce disease [21-23]. Most patients are homozygous for PI*Z; liver disease does not occur in null homozygotes who have severe AAT deficiency but no intra-hepatocytic accumulation. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Hepatic disease'.)

Risk factors for lung disease — Individuals with phenotypes associated with plasma AAT levels below the protective threshold of 11 µmol/L (50 to 80 mg/dL) are considered to have severe AAT deficiency and are at risk for emphysema [24]. The normal plasma concentration of AAT ranges from 20 to 53 µmol/L (150 to 350 mg/dL) (table 1).

Many phenotypes can be associated with severe AAT deficiency, including PI*Null variants, some heterozygous PI*SZ individuals, and PI*M[Heerlen] [6,25]. However, the vast majority of patients are PI*ZZ homozygotes. Plasma AAT levels in these patients cluster tightly around 5 to 6 µmol/L (30 to 40 mg/dL).

Severe deficiency of AAT poses a strong risk factor for early-onset emphysema, but not every severely deficient individual is destined to develop emphysema. Risk factors include cigarette smoking, dusty occupational exposure, a parental history of COPD, and a personal history of asthma, chronic bronchitis, or pneumonia [26,27].

Cigarette smoking increases the risk of developing fixed airflow obstruction and can markedly accelerate the onset of dyspnea by as much as 19 years. In three studies, for example, the age at onset of dyspnea was 48 to 54 years in nonsmokers versus 32 to 40 years in smokers [28-30]. In individuals with the PI*SZ phenotype, cigarette smoking is a particularly important risk factor for the development of COPD, which rarely occurs in nonsmokers with this phenotype [31].

Whether non-smoking PI*MZ heterozygotes are at increased risk of emphysema remains controversial, with available studies showing discordant results:

- In supportive studies, a comparison between individuals in the Lung Health Study with either rapid or slow decline in forced expiratory volume in one second (FEV1) showed that the MZ phenotype was associated with rapid decline (odds ratio 2.8, p=0.03) [32]. Also, a longitudinal study showed a slightly greater annual decrease in FEV1 in individuals with the MZ genotype compared with those who have the MM genotype (25 versus 21 mL/yr, p=0.048) [33]. The odds ratio for developing airflow obstruction was 1.3 in the MZ heterozygotes compared with normal MM homozygotes. The increase in COPD risk among PI*MZ heterozygotes may be limited to those with a symptomatic PI*ZZ first-degree relative [34].

- In an analysis of data from case-control and a multicenter family studies, individuals with PI*MZ, compared to those with PI*MM, had a slightly lower ratios for FEV1/forced vital capacity or FEV1/vital capacity, but no difference in FEV1 [35].

- In contrast, results from a population study of PI*MZ heterozygotes from the Tucson Epidemiologic Study of Airways Obstructive Diseases failed to show any increased risk of developing airflow obstruction in these MZ individuals [36]. Also, a meta-analysis highlights the inconsistency of results from available studies [37], with studies using categorical outcomes generally showing an increased risk and those using continuous measures (eg, FEV1) not showing an excess risk in PI*MZ heterozygotes. Relatively few of the available studies adjusted for smoking status and those that did tended to show a smaller risk (odds ratio 1.61, 95% CI 0.92 – 2.81).

The precise role of occupational exposures in accelerating the loss of lung function in AAT deficiency is also incompletely understood. One study found a link between

self-reported exposure to mineral dust and reduced lung function in PI*ZZ patients [38], while a second trial suggested that agricultural work and the use of domiciliary kerosene are also independently associated with a more rapid loss of lung function [39]. Among New York City Fire Department rescue workers who were exposed to respirable particulates and combustion by-products following the World Trade Center collapse, those with even mild or moderate deficiency of AAT (eg, PI*MZ, PI*SZ, and PI*MS) had a more rapid decline in FEV1 over the next four years than those with normal AAT levels [40].

Clinical presentation of lung disease — The clinical presentation of emphysema due to AAT deficiency has many features in common with usual COPD. Dyspnea is the most common symptom, and many patients report cough, phlegm production, and wheezing, either chronically or with upper respiratory tract infections [30,41-43]. Bronchodilator responsiveness (defined as a post-bronchodilator FEV1 rise of 200 mL and 12 percent) is common in both groups. There are, however, two features of emphysema associated with severe deficiency of AAT that may be distinctive and should lead to suspicion of the diagnosis (table 2):

- The onset of emphysema in AAT-deficient individuals is earlier than that in non-AAT-deficient individuals, who usually present in the sixth and seventh decades of life. In the National Heart, Lung, and Blood Institute-sponsored Registry for Patients with Severe Deficiency of Alpha 1 Antitrypsin, for example, the mean (± SD) FEV1 in 1129 participants was 43 ± 30 percent of predicted and their mean age was 46 ± 11 years [42]. Similarly, an earlier series of 246 PI*ZZ adults found that chronic obstructive pulmonary disease was present in 74.8 percent of the participants, whose median age was approximately 52 years [28].

- Emphysema associated with AAT deficiency often shows a characteristic chest radiographic pattern, in which bullous changes are more prominent at the lung bases than at the apices (picture 1A-B). The prevalence of this pattern of "basilar hyperlucency" varies among series [3,43]. The largest reported series of 165 PI*Z homozygotes examined with plain chest radiographs found that 140 (85 percent) had some radiographic features of emphysema. Virtually all of these patients had emphysematous changes that included the lung bases, and 24 percent had emphysematous changes that were limited to the lung bases. More recent imaging studies have used computed tomography [44,45]. In one study of PI*ZZ individuals, emphysematous abnormalities were most prominent at the bases in 64 percent of patients and at the apices in 36 percent [44]. In another case series examining CT scan findings, emphysematous changes were less prominent overall and more likely to be upper lung zone predominant in PISZ individuals, than PI*Z homozygotes,

despite comparable physiologic impairment [46].

Severe deficiency of AAT has also been associated with **bronchiectasis**. In one study, for example, bronchiectasis was present in 11.3 percent of 246 PI*Z homozygotes [28]. The estimated prevalence in other reports has varied widely from two to 43 percent [47]. The relationship between AAT deficiency and bronchiectasis remains incompletely understood, and the mechanism by which the former could produce the latter is debated. Bronchiectasis seems to occur most commonly in lobes with higher emphysema scores [47]. (See "Clinical manifestations and diagnosis of bronchiectasis in adults".)

There is an uncertain relationship between severe AAT deficiency and **asthma**. Studies have not shown an increased prevalence of AAT deficiency among asthmatics. However, in a large cohort study of over 1000 patients with severe AAT deficiency, 21 percent of patients met diagnostic criteria for asthma [48]. The presence of asthma was not independently associated with an accelerated decline in pulmonary function, and the results of augmentation therapy appear to be similar for asthmatics and nonasthmatic patients with severe AAT deficiency [48].

DIAGNOSIS — The imperative to identify affected individuals becomes stronger with the availability of specific therapy for AAT deficiency. Patients with persistent airflow obstruction on spirometry should be tested. Additional features that should lead clinicians to test for severe AAT deficiency include (table 2) [4]:

- Emphysema in a young individual (eg, age ≤45 years)
- Emphysema in a nonsmoker or minimal smoker
- Emphysema characterized by predominant basilar changes on the chest radiograph
- A family history of emphysema and/or liver disease
- Clinical findings or history of panniculitis
- Clinical findings or history of unexplained chronic liver disease

The diagnosis of severe AAT deficiency is confirmed by demonstrating a serum level below 50 to 80 mg/dL (11 µmol/L) in combination with a severe deficient genotype, generally determined by isoelectric focusing. Genotyping is generally performed on a blood sample using polymerase chain reaction technology or melting curve analysis [49,50]. If the AAT serum level is greater than 80 mg/dL, it is unlikely that the patient has clinically important AAT deficiency. On the other hand, if one is evaluating for the presence of particular mutations, genotyping is necessary to identify heterozygotes and mutations that have incomplete penetrance [50].

Rarely (<4 percent of tests), the results of the AAT serum level and genotyping are discordant. In this case, protein phenotype analysis is performed by isoelectric focusing electrophoresis (available in specialty laboratories) to identify alleles with

abnormal protein migration patterns.

NATURAL HISTORY — Current understanding of the natural history of AAT deficiency is patchy, with some aspects being reasonably clear and others still murky [4].

First two decades of life — Within the first two decades of life, liver dysfunction is the major threat to the health of affected individuals, and pulmonary dysfunction is not a major concern. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Hepatic disease'.)

- In a follow-up study of 15 adolescents identified as PI*ZZ homozygotes at birth in Oregon, all had normal post-bronchodilator spirometry measurements [51]. In support of the benefit of neonatal screening, these subjects had a lower rate of current smoking or of trying smoking than an age-matched cohort.
- Similar findings were noted in a study of 103 PI*ZZ adolescents (aged 16 years) previously found to have AAT deficiency during neonatal screening in Sweden [52]. Compared with an age-matched cohort, the lung function of AAT-deficient adolescents was preserved, and very few (3 percent) of these individuals had ever started smoking.
- A study of PI*ZZ subjects who were detected by screening at birth, demonstrated normal spirometry at age 26 years [53].

Later decades — Beyond the first two to three decades of life, the natural history of individuals with severe deficiency of AAT is less clear. Available estimates of the yearly decline in FEV1 among smokers range from as low as 42 to as high as 317 mL per year, compared with 44 to 110 mL per year in nonsmokers or ex-smokers [3,30,54-58]. The Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin, an NHLBI-sponsored multicenter study of 1,129 patients, found an annual FEV1 decline of 54 mL per year based upon high quality sequential pulmonary function measurements [42,59]. The rate of decline was higher (84 mL per year) among participants with FEV1 between 50 and 79 percent predicted who were not receiving augmentation therapy. Similar findings were reported by the UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) [60].

The prevalence of COPD among subjects with severe AAT deficiency has been estimated to be 75 to 85 percent, with liver disease occurring in 12 to 16 percent. One autopsy study indicated that cirrhosis occurred in 34 percent of decedents, of whom 64 percent had cirrhosis suspected during life [61].

The natural history of AAT deficiency has not been determined using population-based studies. Mortality rates among AAT-deficient individuals that have

been reported using other types of studies [3,28,59,62]:

- A 37 percent mortality rate was observed in an 11-year follow-up study of 246 PI*Z homozygotes [28]. Most deaths were ascribed to respiratory failure (59 percent), with a minority of patients (13 percent) succumbing to complications of liver disease.
- A second follow-up study (up to 7.2 years) noted a consistent 3 percent annual mortality rate among the 1129 enrollees in the NHLBI-sponsored registry [62]. Overall survival over the duration of this study was 82 percent. Most deaths were caused by respiratory failure or liver disease (72 and 10 percent, respectively). Mortality was closely associated with pulmonary function, and was greatest for patients with an FEV1 <15 percent predicted (36 versus 3 percent for patients with FEV1 ≥50 percent predicted).

Studies from the Danish Registry show that, in addition to FEV1, smoking status and method of ascertainment (ie, how the subject comes to the attention of the registry) affect survival [63-65].

- Survival among smokers and among patients with symptoms was lower than among their nonsmoking asymptomatic counterparts [63,65]. Furthermore, asymptomatic nonsmokers, who were usually identified as relatives of symptomatic AAT-deficient individuals, had a survival rate equal to that of the normal age-matched Danish population.
- The FEV1 was a major determinant of survival in AAT-deficient individuals, with the mortality rising exponentially as FEV1 falls below 35 percent of the predicted value (figure 1). As an example, the two-year mortality rate among individuals with FEV1 values of 15 percent predicted was almost 50 percent [64].

Parameters other than FEV1 have been used to predict mortality in patients with AAT-deficiency [66-70]. As an example, decreased lung density as assessed by chest computed tomographic (CT) scan was associated with increased mortality in a group of 256 AAT-deficient individuals followed for five years at a single center [67].

In summary, survival estimates for subjects with severe deficiency of AAT vary among series, presumably due to differences in study populations. Relatively normal survival appears possible for nonsmoking asymptomatic individuals, although survival estimates remain uncertain until long-term follow-up is done in a population-based study [71,72].

The favorable prognosis for this subgroup is consistent with expectations that many

individuals with severe deficiency are asymptomatic and therefore escape medical attention. Patients with established airflow obstruction may derive long-term benefit from AAT augmentation therapy, and, when airflow obstruction and functional limitation is severe, should be considered for lung transplantation. (See "Treatment of alpha-1 antitrypsin deficiency" and "Lung transplantation: General guidelines for recipient selection".)

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SUMMARY AND RECOMMENDATIONS

- Alpha-1 antitrypsin (encoded by the gene PI, MIM +107400) is a member of the serpin family of protease inhibitors. It protects the lower airways from damage caused by the proteolytic enzyme, elastase. (See 'AAT phenotypes' above.)
- The normal alpha-1 antitrypsin allele is the M allele. Over 100 allelic variants have been described, of which the most common severely deficient variant is the Z allele. (See 'AAT phenotypes' above.)
- Severe deficiency of AAT is known to affect approximately 100,000 Americans. However, AAT deficiency is severely under-recognized, with long intervals between the first symptom and diagnosis. (See 'Epidemiology' above.)
- Clinical manifestations of severe deficiency of AAT typically involve the lung (eg, early onset emphysema with a basilar predominant pattern on imaging), liver (eg, cirrhosis), and, rarely, the skin (eg, panniculitis). (See 'Clinical manifestations' above.)
- Patients with persistent airflow obstruction on spirometry should be tested for AAT deficiency. Additional features that should lead to AAT deficiency testing include emphysema in a young individual (eg, age ≤45 years), emphysema in a nonsmoker or minimal smoker, emphysema characterized by predominant basilar changes on the chest radiograph, a family history of emphysema and/or liver disease, current or prior panniculitis, and current or prior unexplained chronic liver disease. (See 'Diagnosis' above.)
- The diagnosis of severe AAT deficiency is confirmed by demonstrating a serum level below 50 to 80 mg/dL (11 µmol/L) in combination with confirmation of a severe deficient genotype, generally determined by isoelectric focusing. (See 'Diagnosis' above.)

- The clinical manifestations of AAT deficiency during the first two to three decades of life is that of liver disease, specifically chronic elevation of liver enzymes or cirrhosis. (See 'Natural history' above.)
- Beyond the first two to three decades of life, patients with severe deficiency of AAT have an accelerated rate of lung function decline, especially with cigarette smoking and some occupational exposures. (See 'Natural history' above.)

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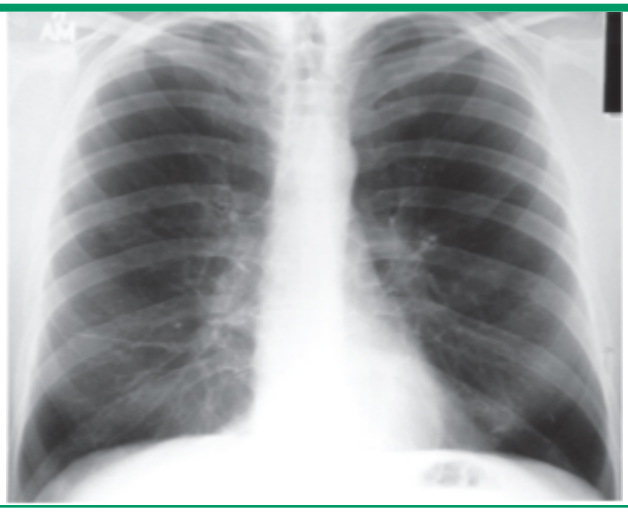
GRAPHICS

Characteristics of alpha-1 antitrypsin deficiency phenotypes

Phenotype	Risk for emphysema	True plasma level, µmol/L	Commercial standard plasma level, mg/dL
MM	No increase	20-53	150-350
MZ	Possible mild increase	12-35	90-210
SS	No increase	15-33	100-140
SZ*	Mild increase (20-50%)	8-19	75-120•
ZZ	High risk (80-100%)	2.5-7	20-45
Null	High risk (100% by age 30)	0	0

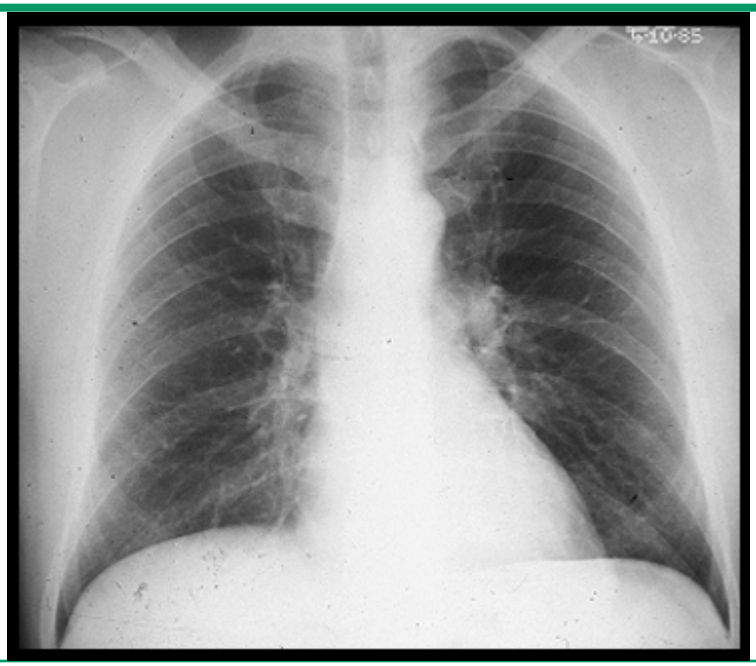
Pulmonary and plasma features of the different phenotypes of alpha-1 antitrypsin deficiency. Standard commercial measures of the plasma concentration overestimate the true level by 35 to 40 percent. * Heterozygotes with the SZ phenotype rarely have evidence of clinical pulmonary disease. • Threshold of 11 µmol/L is approximately equal to a commercial standard level of 80 mg/dL. *Adapted from Official Statement of the American Thoracic Society, Am Rev Respir Dis 1989; 140:1494.*

Emphysema in a1AT



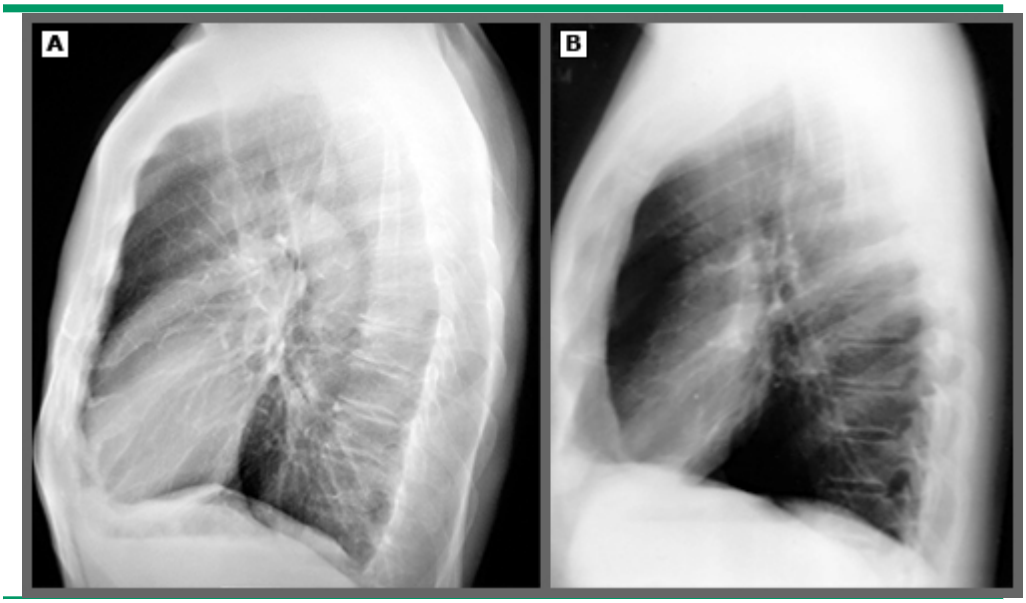
Posteroanterior chest radiograph demonstrating basilar emphysema, with a preferential loss of basilar lung markings, characteristic of alpha-1-antitrypsin deficiency (A1AT). *Courtesy of James K Stoller, MD.*

Normal chest radiograph



Posteroanterior view of a normal chest radiograph.
Courtesy of Carol M Black, MD.

Normal versus emphysema chest radiograph in A1AT

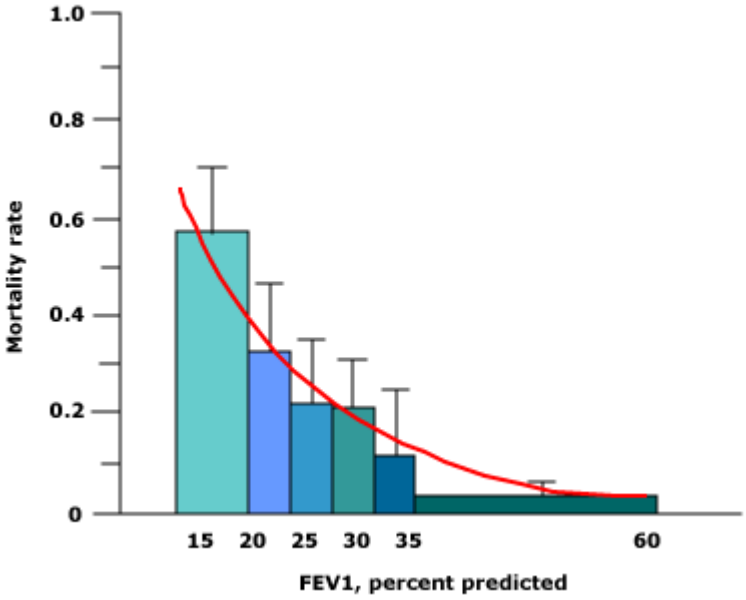


(A) Normal lateral chest radiograph.
(B) Lateral chest radiograph demonstrating hyperinflation with flattened diaphragms and increased retrosternal airspace in a patient with alpha-1-antitrypsin deficiency (A1AT).

Indications of severe alpha-1-antitrypsin deficiency

Emphysema in a young individual (ie, less than or equal to 45 years)
Emphysema in a nonsmoker or minimal smoker
Emphysema characterized by predominant basilar changes on the chest x-ray
A family history of emphysema and/or liver disease, especially unexplained cirrhosis or hepatoma
Clinical findings or history of panniculitis
Clinical findings or history of unexplained chronic liver disease

Survival in AAT according to FEV1



Two year mortality rate in patients with alpha 1-antitrypsin deficiency according to FEV1. Mortality rises dramatically when the FEV1 falls below 35 percent predicted. *Redrawn from Seersholm, N, Dirksen, A, Kok-Jensen, A, Eur Respir J 1994; 7:1985.*

Extrapulmonary manifestations of alpha-1 antitrypsin deficiency

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INTRODUCTION — Alpha-1 antitrypsin (AAT) is a serine protease inhibitor (PI) that is produced in hepatocytes. AAT deficiency is characterized by autosomal co-dominant inheritance of mutations in the alpha 1 antitrypsin gene (MIM 107400) [1]. AAT deficiency is associated with lung, liver, and skin disease.

The extrapulmonary manifestations of AAT deficiency will be reviewed here. The pulmonary manifestations and treatment of AAT deficiency are discussed separately. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency" and "Treatment of alpha-1 antitrypsin deficiency".)

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

HEPATIC DISEASE — Liver disorders, such as neonatal hepatitis, cirrhosis both in children and adults, and hepatocellular carcinoma are associated with some AAT-deficient phenotypes [2-7]. Approximately 10 to 15 percent of newborns are at risk have some form of hepatic disease, and approximately 10 to 15 percent of adults develop hepatic disease [8]. Among never smokers, the prevalence of liver disease at death is higher (28 percent) [9].

The two alleles that are best described to confer risk for liver disease, Z and M(Malton), are associated with accumulation of AAT protein in the hepatocyte. Two other alleles, Null(Hong Kong) and PI Siiyama, are also known to cause intrahepatocytic accumulation. Liver disease has not yet been described in these disorders, but too few individuals have been identified to reach a conclusion [10,11].

Pathogenesis — The pathogenesis of the liver injury in AAT deficiency differs from that of the pulmonary disease. The latter is primarily due to destruction of elastin by elastase, the activity of which is increased because of deficiency of the elastase inhibitor AAT. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency".)

In contrast, liver disease is caused by pathologic polymerization of the variant AAT, resulting in intrahepatocyte accumulation of AAT molecules, rather than a proteolytic mechanism [12-14]. Pathologically, the accumulated AAT appears as inclusions within hepatocytes that stain positively with periodic acid-Schiff (PAS) reagent but resist digestion by diastase (picture 1).

This mechanism of liver disease is supported by two main observations [10]:

- Liver disease has only been observed in individuals with alleles causing intrahepatocyte accumulation, Z and M(Malton).
- Liver disease has not been observed among PI*Null-Null individuals. These patients have no circulating AAT, which predicts the greatest proteolytic risk. However, the liver is not affected because there is no accumulation within the hepatocyte.

Intrahepatocyte accumulation of Z-type molecules occurs within the rough endoplasmic reticulum and results from abnormal folding and aggregation of variant AAT molecules in a mechanism called loop-sheet polymerization [6,15-17]. Factors promoting loop-sheet polymerization include increased temperature and increased concentration of Z-type protein [15]. Polypeptides that inhibit loop-sheet polymerization of variant Z-type molecules are being developed [18].

However, abnormal folding does not explain why only some PI*ZZ individuals develop liver disease. It appears that a second defect is also required: decreased degradation of the Z-type molecules within the endoplasmic reticulum, possibly through defects in the proteasomal or autophagic degradation pathways [19], which further promotes the intrahepatocyte accumulation of AAT [13].

It is unclear how the accumulation of Z-type protein within the rough endoplasmic reticulum causes liver cell injury. Possible mechanisms include simple cell engorgement related to mass build-up, and release of lysosomal enzymes caused by cell engorgement, with resultant cell damage. Some investigators have also

suggested that the PI*ZZ phenotype predisposes to hepatitis and that the liver damage is mediated by viral infection [20].

Risk and natural history — Available data about the risk and natural history of liver disease in AAT-deficient individuals are based primarily on studies of PI*Z homozygotes identified by screening at birth. One study of 200,000 Swedish newborns, for example, found 127 PI*Z homozygotes (prevalence 1/1575) who were then followed into adolescence [2].

- Liver damage occurred in 14 of these neonates (11 percent), most commonly presenting as neonatal hepatitis with cholestasis beginning between four days and four months after birth and persisting for up to 12 months.
- Other clinical presentations among newborns included hepatomegaly with elevated aminotransferase levels (but without hyperbilirubinemia), ascites, and bleeding (often umbilical, superficial, or intracranial [5 percent of affected newborns]).

Follow-up of PI*Z homozygotes identified at birth shows a variable natural history of AAT deficiency-associated liver disease [21].

- Three of 14 children (21 percent) with neonatal hepatitis developed cirrhosis by age seven, two of whom died of complications of cirrhosis.
- By age eight, the remaining 11 children were clinically well but frequently had elevated aminotransferase levels. A few children (14 percent) developed newly elevated values of gamma glutamyl transferase without antecedent neonatal hepatitis.
- Later follow-up at age 12 showed elevated aminotransferase levels in 20 percent of those with icteric neonatal hepatitis and in 14 percent with anicteric hepatitis. However, none of these adolescents had clinically evident liver disease.
- By age 18, only 12 percent had elevations in serum alanine aminotransferase or gamma glutamyl transferase [5].

Others have summarized the natural history of liver dysfunction in children with the PI*ZZ phenotype [22]. Of the 10 to 15 percent of newborns with neonatal hepatitis, 5 percent remained jaundiced and developed progressive cirrhosis with death from complications of cirrhosis within the first year of life. In the remaining children, four clinical patterns of liver evolution were apparent, each occurring in approximately 25 percent of cases:

- Resolution of hepatitis by ages 3 to 10 years without hepatomegaly or

splenomegaly.

- Development of cirrhosis between age six months and 17 years, often causing death from complications of end-stage liver disease.
- Histologic evidence of cirrhosis but with survival through the first decade with few sequelae.
- Persistent elevation of liver function tests without cirrhosis.

Liver disease in adults — Adults with at-risk alleles (eg, Z and M) may develop adult-onset cirrhosis or hepatocellular carcinoma, the former often occurring without antecedent childhood liver disease [9,23,24]. The risk for hepatocellular carcinoma is greater in men (odds ratio 12 compared to controls) than women (odds ratio 8), and hepatocellular carcinoma can occur in the absence of accompanying cirrhosis. (See "Epidemiology and etiologic associations of hepatocellular carcinoma".)

Male gender and obesity also may be risk factors for progression to advanced liver disease in adulthood among patients with severe AAT deficiency [25]. In contrast, alcohol use and viral hepatitis do not appear to increase the risk of progressive hepatic failure [25].

SKIN DISEASE — The major dermatologic manifestation of AAT deficiency, although rare, is necrotizing panniculitis. Other possible dermatologic associations with AAT deficiency include systemic vasculitis, psoriasis, urticaria, and angioedema [8]. (See 'ANCA-positive vasculitis' below.)

Clinical features — Necrotizing panniculitis is characterized by inflammatory lesions of the skin and subcutaneous tissue. [26-29]. The mean age of onset is 40 years old [8]. Patients present with one or more hot, painful, red nodules or plaques on the thigh or buttocks [30]. These lesions can be difficult to distinguish from panniculitis due to other causes, but may be more inflammatory with an oily yellow discharge and more pronounced histologic evidence of acute inflammation (table 1). (See "Weber-Christian disease and other forms of panniculitis".)

Panniculitis is the least common of the well-recognized complications of AAT deficiency, with fewer than 50 cases reported in the English literature [26,29-33]. The prevalence among AAT-deficient subjects is probably less than one case per thousand.

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Pathogenesis — Panniculitis has been reported to occur in a variety of phenotypes, including PI*ZZ, PI*MZ, PI*SS, and PI*MS [30]. Seventy percent of reported cased have occurred in patients with PI*ZZ phenotype and severe AAT deficiency [30]. Similar to the pathophysiology of emphysema in such individuals, the panniculitis is thought to result from unopposed proteolysis in the skin. In a case report, skin biopsy revealed Z type AAT polymers in affected areas, raising the possibility that AAT polymers in the skin contribute to the observed inflammation [34]. Further study is needed before this pathogenetic mechanism is established.

Diagnosis and therapy — As necrotizing panniculitis is a rare manifestation of AAT deficiency, a deep excisional biopsy is usually obtained to establish the diagnosis. Characteristic histologic findings on skin biopsy include lobular fat necrosis of the lower reticular dermis and abundant neutrophil influx interspersed with normal-appearing fat and necrotic panniculus [8].

Based upon the presumed pathophysiologic mechanism of unopposed proteolysis, treatment of panniculitis in AAT-deficient subjects has focused on restoring antiprotease activity. Intravenous infusion of purified AAT has ameliorated the panniculitis in some patients [27,29,30].

Other treatments have included dapsone (100 mg/day for several weeks) and doxycycline (200 mg/day for as long as several months) [27,30,32]. However, evidence in support of these therapies is limited. Doxycycline is believed to act by scavenging reactive oxygen species produced by neutrophils and/or by slowing the breakdown of matrix proteins by elastase. Topical and systemic glucocorticoids have not been helpful [8].

OTHER ASSOCIATIONS — Associations between AAT and vascular disease, inflammatory bowel disease, glomerulonephritis, and vasculitis have been proposed but not definitively established.

Vascular disease — Vascular complications are a less well-established consequence of the PI*ZZ phenotype [35,36]. A number of vascular abnormalities have been suggested, including abdominal and intracranial aneurysms and arterial fibromuscular dysplasia, all based on the principle that unopposed proteolytic activity damages vessel walls in severely deficient individuals [8,30].

In addition, one allele (so-called AAT Pittsburgh) is characterized by substitution of an arginine for a methionine at position 358, causing the protein to mimic the

hemorrhagic effects of antithrombin III [37]. Two individuals with AAT Pittsburgh have thus far been identified, one of whom died of massive bleeding when the acute phase reactant properties of the AAT protein caused levels of the Pittsburgh variant to rise after a viral infection [37].

Inflammatory bowel disease — It has been hypothesized that decreased antiprotease activity in the bowel may promote local injury and progression to inflammatory bowel disease, although data have been conflicting regarding an association between AAT and inflammatory bowel disease [38]. One case control study from Sweden found that significantly more patients with ulcerative colitis were PI*MZ than in the general population (8.5 versus 4.7 percent), and that PI*MZ individuals tended to have more severe colitis [39]. However, a second study from Germany comparing 135 patients with either Crohn's disease or ulcerative colitis with controls found no such associations [40].

Glomerulonephritis — Glomerular disease is an uncommon finding in AAT. Two different types have been described, one related to AAT and the other to the development of liver failure:

- A proliferative glomerulonephritis, most often of the membranoproliferative type, rarely occurs in association with the PI*ZZ phenotype [41,42]. Why this might occur is not clear. Virtually all reported patients have had cirrhosis, suggesting that serious liver disease plays an important role in the development of this immune complex disorder. (See "Classification and causes of membranoproliferative glomerulonephritis".)

- IgA nephropathy occurring in association with hepatic cirrhosis [43]. Glomerular IgA deposition is a common finding in hepatic cirrhosis of any cause, occurring in up to one-third of patients [44]. Impaired removal of IgA-containing complexes (such as those directed against alimentary antigens) by the Kupffer cells in the liver is thought to predispose to IgA deposition in the kidney. One study evaluated 18 children with end-stage liver disease due mostly to AAT deficiency or biliary atresia in whom renal biopsy was performed at the time of hepatic transplantation [43]. Pathologic evidence of either a mesangial proliferative or membranoproliferative glomerulonephritis was seen in all; most patients had IgA nephropathy.

ANCA-positive vasculitis — A putative association between vasculitis and AAT deficiency is based on reports from many countries that AAT variants, both homozygous ZZ and heterozygous Z, occur in higher than expected frequency among individuals with multisystem vasculitides (table 2) [45,46]. (See "Clinical manifestations and diagnosis of Wegener's granulomatosis and microscopic polyangiitis".)

The association between AAT deficiency and C-ANCA positive vasculitis is strengthened by plausible pathogenetic mechanisms. For example, in the extravascular fluid, AAT plays an important role as an inhibitor of proteinase-3, a neutrophil elastase-like serine protease located in the primary granules of the neutrophil. Unchecked, proteinase-3 exerts potent tissue-destructive capacity, so a deficiency of AAT could conceivably trigger an auto-immune response by allowing increased extracellular exposure to proteinase-3 [47]. Alternatively, linkage disequilibrium might promote inheritance of important autoimmunity genes along with abnormal AAT phenotypes [48]. Finally, though unproven, it is conceivable that circulating Z or S polymers could prompt a vasculitic response. (See "Pathogenesis of Wegener's granulomatosis and related vasculitides".)

These findings have prompted a suggestion from the joint American Thoracic Society/ European Respiratory Society in favor of genetic testing for AAT deficiency in individuals with C-ANCA positive vasculitis [8].

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SUMMARY AND RECOMMENDATIONS — Depending on the specific mutation in the alpha 1 antitrypsin (AAT) gene (OMIM 107400), a variety of extrapulmonary manifestations may occur in AAT deficient individuals.

- The types of liver disease associated with AAT deficiency include neonatal hepatitis, hepatomegaly with elevated aminotransferase levels, ascites, cirrhosis, and hepatocellular carcinoma. (See 'Hepatic disease' above.)
- The two AAT alleles most commonly associated with liver disease are Z and M (Malton). The pathogenesis of liver disease in AAT deficient individuals is via accumulation of abnormal AAT protein within hepatocytes. Two rare alleles, Null (Hong Kong) and PI Siiyama, are also known to cause intrahepatocytic accumulation, but it is not known whether they cause clinically significant liver disease. (See 'Hepatic disease' above.)
- Among children with neonatal hepatitis, a quarter will have resolution of hepatitis by age 3 to 10 years without hepatomegaly or splenomegaly; a quarter will develop cirrhosis between age six months and 17 years; often causing end-stage liver disease; a quarter will have histologic evidence of cirrhosis but with few sequelae; and a quarter will have persistent elevation of liver function tests without cirrhosis. (See 'Risk and natural history' above.)
- Adults with these at risk alleles (eg, Z and M) may develop cirrhosis or

hepatocellular carcinoma without antecedent childhood liver disease. (See 'Liver disease in adults' above and "Diagnostic approach to the patient with cirrhosis", section on 'Determining the cause of cirrhosis' and "Clinical features and diagnosis of primary hepatocellular carcinoma", section on 'Diagnosis'.)

- Necrotizing panniculitis, which presents with one or more hot, painful, red nodules or plaques on the thigh or buttocks, is a rare manifestation of AAT deficiency. It occurs in patients with more severe AAT deficiency and those with the PI*ZZ, PI*MZ, PI*SS, and PI*MS genotypes. (See 'Clinical features' above.)

- The usual treatment for panniculitis is intravenous AAT augmentation therapy; dapsone may provide additional benefit. (See 'Diagnosis and therapy' above and "Treatment of alpha-1 antitrypsin deficiency", section on 'Intravenous augmentation therapy'.)

- Associations between AAT and several other disease processes (eg, vascular disease, inflammatory bowel disease, glomerulonephritis, and systemic vasculitis) have been proposed, but not definitively established. (See 'Other associations' above.)

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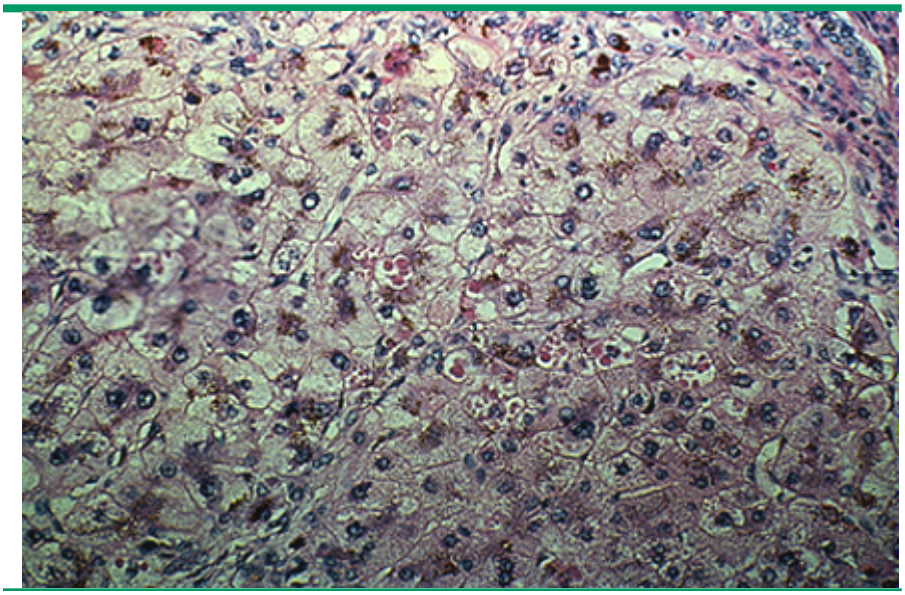
GRAPHICS

Alpha-1-antitrypsin deficiency



High power view of a liver biopsy from a patient with alpha-1-antitrypin deficiency shows numerous intracellular and intercellular PAS-positive granules in the periportal area. *Courtesy of Robert Odze, MD.*

Clinical classification of panniculitis

Idiopathic
Weber-Christian disease
Physical
Cold, thermal injury, trauma, weight loss, chemical exposure
Rheumatologic disorders
Systemic lupus erythematosus (lupus profundus)
Complement deficiency
Rheumatoid arthritis
Other - polymyositis, dermatositis, systemic sclerosis, vasculitis, eosinophilic fascilitis, eosinophilia-myalgia syndrome
Malignancies
Hodgkin's disease and other lymphomas
Cytophagic histiocytic panniculitis
Histiocytosis
Leukemia
Dermatologic diseases
Erythema nodosum
Erythema induratum
Other
Infections
Tuberculosis
Fungal infections
Other
Other disorders

Sarcoidosis, pancreatitis, amyloid, alpha-1-antitrypsin deficiency, renal failure, poststeroid withdrawal, neonatal pannniculitides, lipoatrophy
Factitial

PI phenotypes in anti-PR3 (C-ANCA) positive patients with vasculitic disorders

	France	Sweden	Austria	Australia	UK	Denmark
No. of patients	37	105	32	31	99	44
PI*ZZ	3	1	2	1	1	0
Z allele frequency	17.6	9	10.9	6.5	5.6	9.1
Z allele in controls	1.9	2.4	1.4	0.9	1.8	2.4

Data from: Esnault, VL, Testa, A, Audrain, M, et al. Alpha-1 antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. Kidney Int 1993; 43:1329. Reproduced with permission from: American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003; 168:818. Official Journal of the American Thoracic Society. Copyright © 2003 American Thoracic Society.

Treatment of alpha-1 antitrypsin deficiency

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INTRODUCTION — Severe deficiency of alpha-1 antitrypsin (AAT) is associated with early onset pulmonary emphysema and with several forms of liver disease, including cirrhosis, neonatal hepatitis, and hepatocellular carcinoma. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency" and "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency".)

The discovery of the structure and function of the AAT protein, and its subsequent isolation and purification, have allowed replacement therapy (so-called "augmentation therapy") aimed at preventing progression of the associated lung disease [1,2]. Isolation of the gene and advances in gene therapy further broadened the potential for specific therapy.

The normal plasma levels of AAT are 20 to 53 µmol/L (100 to 220 mg/dL by nephelometry). Population studies suggest a minimum plasma threshold of 11 µmol/L (corresponding to 80 mg/dL in some assays and 50 mg/dL by nephelometry), below which there is insufficient AAT to protect the lung, leading to a risk of developing emphysema. Most patients below this threshold level have the Pi*Z (protease inhibitor Z) phenotype (table 1). For other phenotypes that describe a range of plasma levels that straddle the 11µmol/L "protective threshold," the plasma levels should be used as a guide for considering augmentation therapy. A review of the different AAT alleles is discussed elsewhere. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency".)

The current goal in the treatment of AAT deficiency is to raise the plasma AAT level (and therefore the concentration of AAT in the lung interstitium) above the protective threshold. Three major approaches have been considered to achieve this goal:

- Intravenous or aerosolized augmentation therapy

- Enhancement of endogenous alpha-1 antitrypsin production
- Gene therapy

The only one of these approaches that is currently approved and available is intravenous augmentation therapy. Organ transplantation is another option for patients with end-stage lung or liver disease.

INTRAVENOUS AUGMENTATION THERAPY — Intravenous augmentation via the infusion of pooled human AAT (alpha-1 antiprotease) is currently the most direct and efficient means of elevating AAT levels in the plasma and in the lung interstitium [3,4].

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

Clinical efficacy — Limited data are available regarding the clinical efficacy of intravenous AAT. Infusion therapy appears to be safe, well tolerated, and without significant side effects [5]. Infusions of intravenous AAT can effectively augment plasma and epithelial lining fluid (ELF) levels of AAT and anti-neutrophil elastase activity [6]. However, reliance upon plasma values alone to guide dosing raises the following serious concerns:

- The protective threshold levels of AAT in plasma and ELF reflect estimates of values that separate affected from unaffected individuals. Because a "true" protective threshold value is not available, the amount of augmentation needed to prevent or retard disease is not precisely known.
- As some severely deficient patients have normal lung function, it is apparent that plasma levels alone do not predict disease, but only assign a risk for developing disease.

Given these concerns, the ideal way to study the clinical efficacy of augmentation therapy would be a randomized, placebo-controlled clinical trial of deficient patients with and without clinical disease followed prospectively over a long period of time. In a randomized trial, 77 PI*ZZ phenotype patients received weekly infusions of human AAT or placebo for approximately two years [5]. Computed tomography densitometry showed a trend toward treatment benefit, although the exacerbation frequency and pulmonary function were not affected. This confirmed similar results from an earlier trial [7]. A meta-analysis of randomized and nonrandomized studies included 1509 patients and found that augmentation had a modest effect in slowing lung function decline [8]. In contrast, a systematic review of the two small randomized trials suggested little improvement in patient important outcomes [9].

Additional randomized trials are in progress.

The results of some observational studies not included in the Cochrane meta-analysis support the clinical efficacy of augmentation therapy [9]:

- The National Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin conducted a multicenter, prospective cohort study of 1129 patients sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health (NHLBI) [10]. Survival was enhanced in recipients of augmentation therapy compared with non-recipients [11]. In the subset of patients with FEV1 35 to 49 percent predicted, the rate of FEV1 decline was also slowed in recipients of augmentation therapy.
- A second study compared the rate of FEV1 decline among 97 Danish former smokers with severe alpha-1 antitrypsin deficiency who did not receive augmentation therapy with the rate of decline in 198 severely deficient German former smokers who received weekly infusions (60 mg/kg) over a mean of 3.2 years [12]. Overall, the rate of decline of FEV1 was lower among the treated patients than among the untreated (-53 mL per year versus -75 mL per year, p=0.02).
- A longitudinal study following 96 patients with severe alpha-1 antitrypsin deficiency analyzed the rate of decline in FEV1 before and after weekly augmentation therapy [13]. In distinction to the two large observational studies discussed above, this study showed that the rate of decline in FEV1 during augmentation therapy was slowest in those patients with mild airflow obstruction.

To the extent that the results of the two observational studies above are concordant, they strengthen support for the clinical efficacy of intravenous augmentation therapy. Effect size estimates based upon the observational data from the NHLBI registry suggest that randomized trials of augmentation therapy may be possible with as few as 128 patients per treatment arm (using FEV1 as an outcome measure) and 83 patients per treatment arm (using mortality as an outcome measure) [14]. However, these findings assume that effect sizes in a randomized trial will resemble those in an observational study. To date, no definitive randomized trial of adequate size has demonstrated the clinical efficacy of augmentation therapy.

Selection of patients — Recommendations from different official organizations predate some studies of augmentation therapy and vary [10-12]. The American Thoracic Society suggests weekly augmentation therapy with human pooled AAT for individuals who have plasma levels of AAT less than 11 µmol/L and established airflow obstruction, defined as an FEV1 <80 percent predicted [15,16].

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In comparison, the Canadian Thoracic Society suggests reserving AAT augmentation therapy for AAT-deficient patients with impaired FEV1 of 35 to 50 percent predicted who have quit smoking and are on optimal medical therapy, but continue to show a rapid decline in FEV1 [17,18].

When intravenous augmentation therapy is entertained, proper patient selection is essential. The selection criteria include:

- High-risk phenotype
- Plasma AAT level below 11 μmol/L
- Airflow obstruction by spirometry
- Likely compliance with the protocol
- Age equal to or greater than 18 years
- Nonsmoker or ex-smoker

Augmentation therapy is **not** recommended for patients with heterozygous phenotypes whose plasma AAT level exceeds 11 μmol/L [19]. Controversy exists regarding the administration of augmentation therapy in two other groups of patients:

- Patients with severe degrees of fixed airflow obstruction — Advocates suggest that defending against any decrement in lung function is important in these patients. On the other hand, opponents suggest that established, severe chronic obstructive pulmonary disease (COPD) lessens the benefit of augmentation therapy and that the efficacy of therapy in preventing loss of the little remaining FEV1 is negligible. A lower limit of FEV1 below which augmentation therapy should be withheld has not been proposed, although available studies do not show clinical efficacy in patients with severe airflow obstruction (eg, FEV1 <30 percent predicted).

- Patients with normal airflow but radiographic (especially CT) evidence of emphysema — Optimal therapy in this setting is uncertain. One approach is to follow these patients closely, eg, every six months, with outpatient visits and full pulmonary function tests (spirometry, lung volumes, diffusing capacity, and arterial blood gases) in order to ascertain early declines in airflow, at which time augmentation therapy can be begun.

Schedules of administration — Weekly, biweekly, and monthly intervals for intravenous augmentation therapy have been studied. Currently, weekly infusions

are the only Food and Drug Administration-approved regimen. Available studies suggest that a weekly infusion schedule maintains serum levels of AAT above the protective threshold more consistently than does biweekly or monthly therapy, although no differences in clinical efficacy of different augmentation therapy schedules have been observed.

In the initial study, weekly infusions of 4 grams of purified human AAT were given to five PI*ZZ patients for four weeks [6]. This trial provided several pieces of important information:

- AAT levels could be augmented by intravenous infusion.
- Trough levels could be maintained above the protective threshold.
- Infused AAT diffused into lung tissue, elevating epithelial lining fluid (ELF) levels.
- Anti-neutrophil elastase activity was preserved in vivo after infusion.
- Intravenous administration of pooled human AAT was safe.

Subsequent studies have confirmed that weekly infusions of human pooled AAT at a dose of 60 mg/kg maintain AAT levels in plasma and ELF above the protective threshold, both throughout the week and over the long-term (figure 1) [1,2,20].

Although effective, weekly infusions and the higher associated administration costs can be difficult for patients and support staff. To reduce the frequency of treatment, the efficacy of giving larger doses less often has been studied. A preliminary study in a single patient has shown that biweekly infusions of AAT at twice the infusion dose used for weekly administration (120 mg/kg versus 60 mg/kg) can maintain plasma and ELF levels above the protective threshold [21]. However, a subsequent series of 23 patients suggests that simply doubling the dose may not be sufficient [22]. In this report, trough plasma AAT and ELF levels were suboptimal at 120 mg/kg; pharmacokinetic modeling suggested that a dose of 200 mg/kg could be required for biweekly infusions [22]. Overall, persisting uncertainties about the benefits of infusion frequencies less often than once weekly lead these authors to favor once weekly infusions.

In comparison, monthly infusions are biochemically effective. In one study of nine patients with AAT deficiency (8 PI*ZZ and 1 PI*Z Null), monthly infusions of human pooled AAT at a dose of 250 mg/kg (ie, four times the weekly infusion dose) effectively raised plasma and ELF AAT levels (figure 2), as well as anti-neutrophil elastase activity above the protective thresholds [23]. This effect was maintained until the next dose and over the long-term. This study was subsequently extended as monthly infusions were given for up to 24 months in eight severely deficient patients [2].

Side effects — Side effects associated with intravenous AAT infusion have been

uncommon, and no long-term reactions have been noted to date. Although the current AAT product is a pooled human plasma derivative, no cases of HIV or hepatitis transmission or of viral antibody development in recipients have been reported [2,6]. (See "Viral inactivation of blood products".)

There are, however, some problems that can occur:

- Low-grade fever and mild flu-like symptoms are infrequent and usually self-limited.
- Anaphylaxis with IgE antibody formation to AAT has been reported, but is extremely rare [24].
- A syndrome of transient fever, chest and low back pain, and thrombocytopenia has been described in a few individuals. This syndrome is due to a high molecular weight contaminant in the stabilizer added to the AAT product in the late 1980s [2].
- Several lots of Prolastin® (human pooled AAT, Talecris Biotherapeutics, Inc) were withdrawn from the market when it was discovered that some of the intermediates used to produce the drug derived from two individuals diagnosed with Creutzfeldt-Jakob disease (CJD). However, there have been no reports of human-to-human transmission of CJD through blood products, and there is no known association between blood transfusion and the development of CJD [25]. Thus, the risk to recipients is deemed very low. However, because a reliable serologic test for CJD does not yet exist, only long-term follow-up of recipients of the tainted Prolastin® will establish the true magnitude of the risk. (See "Creutzfeldt-Jakob disease" and "Viral inactivation of blood products".)
- Pooled human plasma alpha 1-antiprotease contains small amounts of IgA, so that IgA-deficient individuals with anti-IgA antibodies are at risk of anaphylaxis with current infusions. Prior to initiating intravenous AAT therapy, we check for IgA deficiency or anti-IgA antibodies prior to administration of human pooled AAT, although these reactions are rare. (See "Selective IgA deficiency: Clinical manifestations, pathophysiology, and diagnosis", section on 'Anaphylactic reactions to blood products' and "Immunologic blood transfusion reactions", section on 'Anaphylactic reactions'.)

Investigators from The National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin reported the Registry experience with adverse reactions to augmentation therapy [26]. The overall incidence of adverse events was 0.02 per patient-month of treatment. Most events were of moderate severity, and included dizziness, chest tightness, rash, hives, and

fever. A small number of severe adverse effects, including wheeze, hypotension, and loss of consciousness were reported. Over 80 percent of patients involved in the survey reported no adverse events associated with treatment.

Dosage — The dose of purified pooled human antiprotease depends on the intervals between treatments. The dose for weekly infusions is 60 mg/kg and for monthly infusions is 250 mg/kg. The recommended protocol for intravenous AAT augmentation therapy is summarized in the table (table 2). Some clinicians prefer monthly therapy, although weekly therapy is the only FDA-approved interval.

Formulation and administration — Three AAT products are available, Aralast®, Prolastin®, and Zemaira®, and are supplied in a powdered, lyophilized form. The directions for reconstitution provided in the package insert should be followed closely. After reconstitution, pooled AAT should be used within three hours. The infusion rate is typically 0.08 mL/kg body weight per minute, such that the average weekly infusion takes 15 minutes (table 2). Emergency equipment (including epinephrine) should be immediately available during the infusion. The infusion rate may need to be reduced or interrupted if the patient develops an adverse event.

Cost — Cost is an important issue given the lack of studies proving clinical efficacy [27]. The true cost of alpha-1 antitrypsin deficiency has been compared to the cost of other chronic diseases. The estimated mean annual costs for patients receiving augmentation therapy are up to approximately $80,000 per year, three times the annual cost for patients with COPD [28,29].

Several cost-effectiveness analyses have assessed the incremental cost per year of life saved for weekly augmentation therapy and estimates have varied depending on methodologic differences in the analyses [30,31]. Though the incremental cost-effectiveness estimates for augmentation therapy exceed the values usually accepted for widely implemented interventions in health care (eg, >$300,000 per quality adjusted life-year versus values of <$50,000 per quality adjusted life-year for hemodialysis, etc), the authors [31] favored continued use of augmentation therapy as it represents the only currently available specific therapy for AAT deficiency, at least until most cost-effective future alternatives are available.

SUPPORTIVE THERAPY — Supportive therapy for patients with airflow obstruction follows the guidelines for the management of COPD. (See "Management of stable chronic obstructive pulmonary disease".)

The following components should be included (table 2):

- Avoidance of cigarette smoking.
- Maximal supportive therapy with bronchodilators (such as beta agonists), inhaled or oral glucocorticoids, pulmonary rehabilitation, nutritional support,

and oxygen (if indicated) [32].

- Prompt treatment of lower respiratory tract infections to minimize the inflammatory cell burden in the lung.
- Preventive vaccination (eg, influenza and pneumococcal vaccines).
- Although transmission of HIV or hepatitis B virus (HBV) with human pooled AAT has not been reported, baseline HIV and HBV titers should be obtained. It has been recommended that patients without anti-HBV antibodies should be immunized, though fewer clinicians appear to be offering such vaccination before initiating augmentation therapy without reported adverse sequelae. If it becomes necessary to treat a patient with intravenous augmentation therapy before an adequate antibody response to vaccination can be achieved, a single dose of hepatitis B immune globulin (0.06 mL/kg) can be given with the first dose of hepatitis B vaccine [15].

EXPERIMENTAL THERAPIES

Aerosolized AAT — Direct delivery of AAT to the lung by inhalation has been an attractive alternative to intravenous infusion because of a number of potential advantages:

- The site of clinical damage is directly targeted.
- Less drug is required than with intravenous therapy (in which only 2 percent of the drug reaches the lung [33]); as a result, aerosolized therapy is much less expensive.
- Intravenous access is not required.
- Recombinant AAT, whose short half-life (minutes) when administered systemically precludes intravenous infusion, may be effective when delivered as an aerosol (see below).
- Inhaling aerosolized medications is more familiar to patients with emphysema and to many clinicians.
- Patients can self-administer the drug.

The few available studies of aerosolized AAT have used either human pooled AAT (pAAT) or recombinant AAT (rAAT). Both human and animal studies have shown that pAAT can be aerosolized to a particle size sufficiently small to enter the lower respiratory tract [34-36]. In one study, for example, aerosolized pAAT was given in a dose of 100 mg every 12 hours to 12 patients with AAT deficiency (11 PI*ZZ, 1 PI* null) for one week [34]. The plasma and ELF levels were significantly elevated

above the protective threshold; the aerosolized protein was functionally intact as evidenced by normalization of ELF antineutrophil elastase activity (figure 3). There were no ill effects observed, including induced or prolonged bronchospasm.

Recombinant AAT (rAAT) is an attractive alternative to pAAT because it can be produced in large quantities without the risk of viral contamination. rAAT is a 45 kilodalton protein produced by transformed yeast containing a plasmid with the human cloned DNA sequence for normal human AAT. Its structure is identical to that of pAAT except that it lacks the three carbohydrate side chains present in the native plasma protein [37].

The initial animal studies evaluating the use of rAAT for intravenous administration found that it has a much shorter half-life than pAAT due to rapid renal clearance, a consequence of the missing carbohydrate side chains on the rAAT protein. However, preliminary studies have shown that conjugating the molecule to polyethylene glycol can reduce renal clearance [37]. Although anti-neutrophil elastase activity was decreased in the modified molecule by 12 to 33 percent, rAAT may be usable for intravenous infusion in the modified form in the future.

Aerosolized rAAT, with its direct delivery to the lung, avoids the problem of the short plasma half-life. Using the same approach as with pAAT, rAAT has been shown to be safe for human use without clinical or immunologic side effects. It reaches the ELF as a structurally and functionally intact molecule and raises the AAT levels in the lung in a manner similar to pAAT [38]. However, this form of therapy is still under evaluation, and no clinical studies are yet available.

Intravenous recombinant AAT — The use of recombinant DNA-produced AAT (rAAT) derived from transgenic sheep has been studied [30]. However, the presence of very small amounts of sheep AAT and sheep alpha-1 antichymotrypsin in purified rAAT has been linked to high rates of allergic sensitization and impaired pulmonary function. In a preliminary report, 24 percent of patients (10 of 41) treated with aerosolized rAAT developed an antibody response to sheep AAT, and nearly 80 percent of patients (32 of 41) generated antibodies to sheep alpha-1 antichymotrypsin [31]. Four patients dropped out of the study because of worsening pulmonary function, three of whom became sensitized to both sheep-derived contaminants over the course of their treatment. These findings suggest that immune-mediated toxic effects remain a significant barrier to the clinical use of rAAT.

Enhancement of endogenous AAT production — The observation that AAT is an acute phase reactant that increases with fever, shock, trauma, and pregnancy has led to a variety of pharmacologic strategies to augment plasma AAT levels [39,40]. Hormonal derivatives, such as danazol, tamoxifen, and estrogen/progesterone combinations, have all been tried with limited success. Since

the relatively small elevation is inadequate to reach the protective threshold in deficient patients, pharmacologic treatments to increase endogenous production of AAT have been largely discarded for PI*Z homozygotes [41-43].

Transgenic mouse models of the PI*ZZ phenotype of AAT deficiency suggest that 4-phenylbutyric acid (PBA) may be of potential benefit. An abstract noted that oral administration of PBA to such mice caused an increase in plasma concentrations of AAT to approximately one-half those found in strains that are transgenic for the wild type AAT genotype [44]. PBA has been used safely as an ammonia scavenger in humans with urea cycle disorders, and appears to exert its effects in PI*ZZ AAT-deficient patients by reversing the misfolding of AAT that results in accumulation in the endoplasmic reticulum of hepatocytes rather than secretion into the bloodstream. However, a randomized controlled trial of 4-PBA did not suggest efficacy in that serum levels of AAT were not increased in 4-PBA recipients [45].

Gene therapy — Gene therapy represents the exogenous transfer of DNA which codes for normal AAT to deficient human cells, allowing for ongoing endogenous production to augment the deficient levels [4]. cDNA can be packaged into the genome of viruses whose native genome has been depleted of regions which modulate viral replication [46]. These "replication-deficient viruses" can "infect" or integrate their genome into host cells, allowing the host cell to manufacture AAT using host protein synthetic mechanisms.

The initial studies of gene transfer of the AAT gene were accomplished using retroviruses to infect harvested cells in vitro (fibroblasts or hepatocytes) [47]. Implantation or infusion of the modified cells into the host animal resulted in the production of human AAT with significantly elevated plasma and ELF levels. However, expression of the gene was limited and the amount of AAT produced was inadequate to raise plasma levels above the protective threshold.

Other studies have used the adenovirus vector for transfer and expression of the AAT gene in tracheal, vascular, and peritoneal cell targets [48-50], or directly introduced AAT DNA into pulmonary macrophages via the mannose receptor [51]. Once again, plasma and ELF levels of AAT were below the protective thresholds.

An in vivo study examined the response of nine AAT deficient patients to intramuscular injection of a recombinant adeno-associated virus (rAAV) vector expressing normal AAT [52]. After the injection, normal AAT was expressed above background, but below the level usually associated with a therapeutic effect.

A different in vivo study using a novel plasmid-cationic liposome complex as a nonvirus-mediated transfer technique has successfully delivered the normal alpha-1 antitrypsin gene to the respiratory epithelium of deficient patients, producing

potentially therapeutic local alpha-1 antitrypsin concentrations [53]. Unfortunately, current studies suggest that the duration of gene expression may be finite, because exogenously induced genes are inactivated over time by host cell mechanisms that are not yet fully understood [4].

Most recently, human studies using an adeno-associated virus vector to transfect human muscle have been initiated. While promising, the results are too preliminary to judge efficacy [54].

LUNG VOLUME REDUCTION SURGERY — Lung volume reduction surgery (LVRS, also called reduction pneumoplasty or bilateral pneumectomy) is a surgical technique entails reducing the lung volume by wedge excision of emphysematous tissue. Assessment of the response of 10 AAT deficient patients to LVRS found that these patients had a higher two year mortality, than patients randomized to medical therapy [55]. In addition, AAT deficient patients had a smaller increase in exercise tolerance and a smaller and less sustained improvement in FEV1, compared with patients who were alpha-1 antitrypsin replete. Statistical analysis was limited due to the small sample size, but this observation suggests caution in recommending LVRS for AAT deficient patients. (See "Lung volume reduction surgery in COPD".)

LUNG AND LIVER TRANSPLANTATION — Advances in solid organ transplantation have made lung and liver transplantation available as therapeutic options for AAT deficient patients. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Hepatic disease' and "Lung transplantation: General guidelines for recipient selection", section on 'Chronic obstructive pulmonary disease (COPD)'.)

Liver transplantation has been reserved for patients with end-stage hepatic disease. It has the additional advantage of correcting the AAT deficiency, because the normal phenotype donor liver produces and secretes AAT. (See "Patient selection for liver transplantation".)

Augmentation following lung transplantation — Augmentation therapy following lung transplantation is controversial because it is costly and lacks proven efficacy [56]. In addition, it might not improve outcome or longevity during the patient's lifetime, since recurrent emphysema is unlikely to occur for 30 to 40 years in the absence of smoking. Most transplant centers currently do not give augmentation therapy to lung transplant recipients who have AAT. In one study of 134 such patients, only 19 percent were receiving augmentation therapy [57].

Proponents of therapy suggest that the inflammatory and infectious milieu of the posttransplant lung may cause accelerated elastin breakdown. The demonstration of free elastin in bronchoalveolar lavage fluid during periods of acute infection and

rejection is consistent with this hypothesis [58].

One approach is to resume intravenous augmentation therapy if characteristic radiologic changes of emphysema develop in the transplanted lung. In addition, it may be advisable to provide once-weekly therapy (60 mg/kg) during conditions associated with an increased neutrophil burden in the lung (as with pneumonia or acute rejection) [56].

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

SUMMARY AND RECOMMENDATIONS

- Severe deficiency of alpha-1 antitrypsin (AAT) is associated with both early onset pulmonary emphysema and several forms of liver disease, including cirrhosis, neonatal hepatitis, and hepatocellular carcinoma. (See 'Introduction' above.)
- The normal plasma level of AAT is 20 to 53 micromol/L (100 to 220 mg/dL by nephelometry). Patients with a plasma level below 11 micromol/L (corresponding to 80 mg/dL in some assays and 50 mg/dL by nephelometry) are at increased risk of developing emphysema. (See 'Introduction' above.)
- Cessation of cigarette smoking is of key importance for individuals with AAT deficiency who smoke. (See "Patient information: Quitting smoking" and "Management of smoking cessation in adults".)
- Guidelines issued by the American Thoracic Society suggest intravenous supplementation with pooled human alpha-1 antiprotease (AAT) for individuals who have a high-risk phenotype (eg, PiZZ), a plasma AAT level below 11 micromol/L, airflow obstruction by spirometry, likely compliance with the protocol, and age equal to or greater than 18 years (table 2). (See 'Selection of patients' above.)
- Baseline HIV and hepatitis B virus (HBV) titers are typically obtained before initiating AAT augmentation; patients without anti-HBV antibodies are immunized to HBV. (See 'Side effects' above.)
- Pooled human plasma AAT contains small amounts of IgA, so the risk of anaphylaxis is increased in IgA-deficient individuals with anti-IgA antibodies. Anaphylaxis mediated by development of IgE antibody to pooled human plasma AAT is rare. (See 'Side effects' above.)
- Supportive therapy for patients with emphysema due to AAT deficiency follows

the usual guidelines for COPD and includes smoking cessation, prompt treatment of lower respiratory tract infections to minimize the inflammatory cell burden in the lung, and preventive vaccination (eg, influenza and pneumococcal vaccines). (See 'Supportive therapy' above and "Management of stable chronic obstructive pulmonary disease".)

- The experience with lung volume reduction surgery (LVRS) for patients with AAT deficiency is limited, but thus far LVRS has not been shown to improve survival compared with medical therapy. Both the duration and magnitude of the increase in forced expiratory volume in one second (FEV1) experienced by AAT deficient individuals following LVRS are more modest than that of patients with COPD and normal AAT levels. (See 'Lung volume reduction surgery' above.)

- Liver transplantation is reserved for patients with end-stage hepatic disease. After liver transplantation, the AAT deficiency is corrected, because the normal phenotype donor liver produces and secretes AAT. (See 'Lung and liver transplantation' above.)

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

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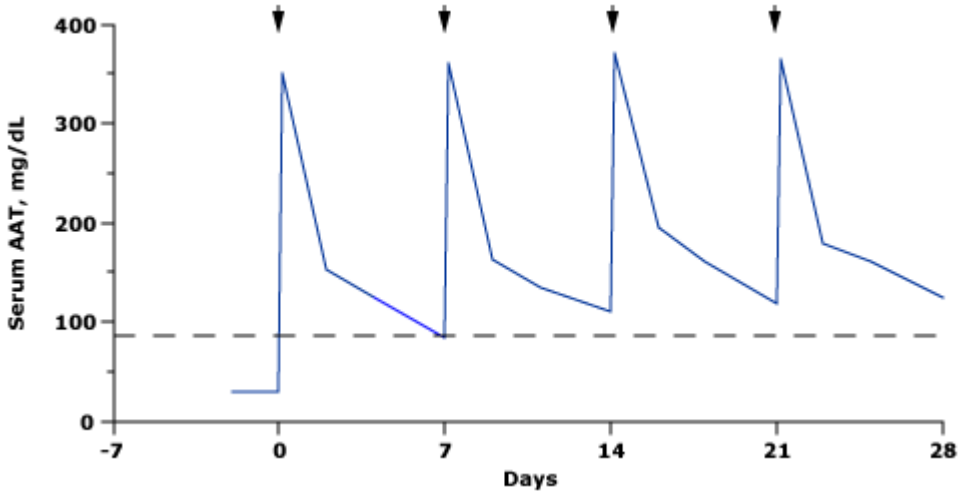
GRAPHICS

Characteristics of alpha-1 antitrypsin deficiency phenotypes

Phenotype	Risk for emphysema	True plasma level, µmol/L	Commercial standard plasma level, mg/dL
MM	No increase	20-53	150-350
MZ	Possible mild increase	12-35	90-210
SS	No increase	15-33	100-140
SZ*	Mild increase (20-50%)	8-19	75-120•
ZZ	High risk (80-100%)	2.5-7	20-45
Null	High risk (100% by age 30)	0	0

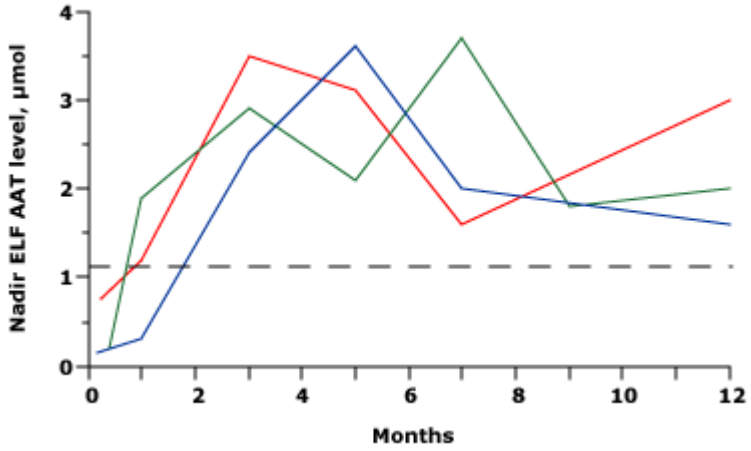
Pulmonary and plasma features of the different phenotypes of alpha-1 antitrypsin deficiency. Standard commercial measures of the plasma concentration overestimate the true level by 35 to 40 percent. * Heterozygotes with the SZ phenotype rarely have evidence of clinical pulmonary disease. • Threshold of 11 µmol/L is approximately equal to a commercial standard level of 80 mg/dL. *Adapted from Official Statement of the American Thoracic Society, Am Rev Respir Dis 1989; 140:1494.*

Efficacy of weekly infusions of alpha-1 antitrypsin



Serum alpha-1 antitrypsin (AAT) levels after once weekly administration of 60 mg/kg of active AAT to patients with the ZZ homozygous form of AAT deficiency. The dashed line represents the protective threshold. Weekly infusions (arrows) maintained the serum A1AT levels above this threshold. Values are in commercial standard units of mg/dL; the true standard levels in µmol/L can be obtained by dividing the commercial standard value by 7.3. *Redrawn from Hubbard, RC, Crystal, RG, Am J Med 1988; 84(Suppl 6A):52.*

Maintenance of adequate ELF antitrypsin activity with monthly infusions



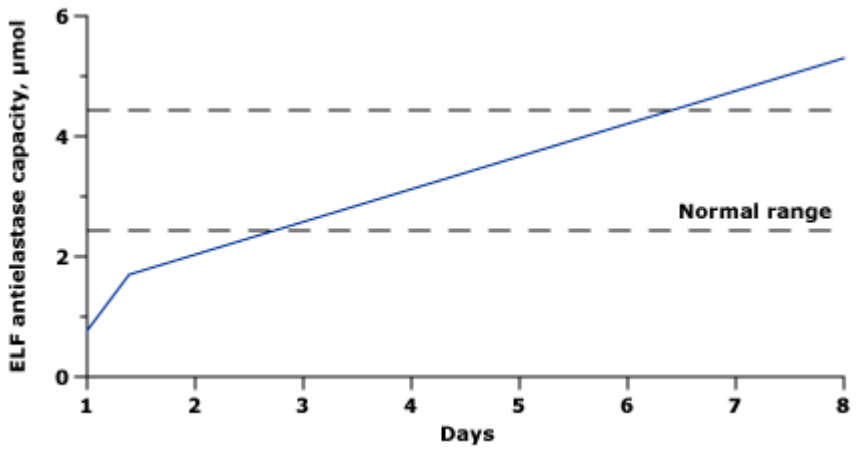
Effect of monthly infusions of 250 mg/kg of alpha-1 antitrypsin (AAT) on epithelial lining fluid (ELF) levels of AAT in three patients. The AAT levels are based upon a true laboratory standard. The dashed line represents the theoretical protective threshold. AAT levels were maintained above this threshold with monthly infusions.
Redrawn from Hubbard, RC, Sellers, S, Czerski, D, et al, JAMA 1988; 260:1259.

Intravenous augmentation therapy with alpha-1-antiprotease

Pre-procedure testing
Spirometry with DLCO
Hepatitis profile
Liver function tests
HIV titer*
Immunizations*
Hepatitis B
First dose at time of initial infusion
Repeat dose at 1 and 6 months
Anti-hepatitis B immunoglobulin
Dose: 0.06 mL/kg IM once
Supportive therapy
Cessation of smoking
Avoidance of respiratory irritants
Combination bronchodilators
Pulmonary rehabilitation
Oxygen therapy (as needed)
Treatment of respiratory infections
Influenza and pneumococcal vaccinations
Protocol for monthly augmentation therapy
Product: Pooled plasma-derived alpha 1-antiprotease
Interval: Weekly, biweekly, monthly
Dose: ___ mg/kg, 60 mg/kg (weekly) or 250 mg/kg (monthly)
Weight: ___ kg
Infusion rate depends on specific products used. Consult package insert.

* Variable practice.

Efficacy of aerosolized alpha-1 antitrypsin



Effect of aerosolized alpha-1 antitrypsin (100 mg every 12 hours) on epithelial lining fluid (ELF) antineutrophil elastase capacity. Replacement therapy raised ELF antielastase capacity into the normal range. The linear relationship between days 1 and 7 is illustrative and not necessarily representative of the real changes that occurred. *Redrawn from Hubbard, RC, Brantly, ML, Sellers, SE, et al, Ann Intern Med 1989; 111:206.*